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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/26/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/019,501	OGATA ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/29/08; 8/5/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,7-10,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 7-10, 25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 4, 7-10, 25 and 26 are pending.

2. In view of the amendment filed August 29, 2008 and August 5, 2008 the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 4, 7-10, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of treating at least one symptom selected from the group consisting of polyuria, dehydration, mouth dryness and hyperosmolarity caused by a decrease in vasopressin level in blood comprising administering to a patient at least one humanized or monoclonal antibody or binding fragment thereof that binds to parathyroid hormone related protein of SEQ ID NO: 75, wherein the antibody or binding fragment thereof inhibits the binding of PTHrP to its receptor, and neutralizes the activity of said parathyroid hormone related protein, (2) a method of increasing vasopressin level in blood of a patient comprising administering to said patient at least one humanized or monoclonal antibody or binding fragment thereof that binds to parathyroid hormone related protein of SEQ ID NO: 75, **does not** reasonably provide enablement for any methods as set forth in claim 4 wherein the antibody is any modified antibody, any modified antibody having any amino acid substitutions or chemical modification and a method of inhibit a decrease vasopressin level in blood of a patient as set forth in claims 4, 7-10, 25 and 26. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claim 4 encompasses a method of inhibit *a decrease or increasing vasopressin* level in blood comprising administering to a patient at least one humanized anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody, or binding fragment thereof that binds specifically to SEQ ID NO: 75, wherein the humanized antibody is a modified antibody having any amino acid substitution or chemical modification.

The specification discloses only a method of ameliorating at least one symptom caused by a decrease in blood vasopressin level comprising administering to a patient at least one humanized monoclonal anti-parathyroid hormone related protein 1-34 (anti-PTHrP (1-34)) antibody or binding fragment thereof wherein the binding of said antibody or binding fragment thereof to parathyroid hormone related protein 1-34 of SEQ ID NO: 75 inhibits the binding of parathyroid hormone related protein 1-34 to its receptor and thereby ameliorate at least one symptom is caused by low blood vasopressin level, see page 23-23, Figure 1. The specification discloses the use of a hypercalcemia model of nude rat implanted with human large cell lung carcinoma LC-6 to evaluate the humanized monoclonal antibody (anti-PTHrP (1-34)) on the effects of low blood vasopressin levels. The hypercalcemia model animals were shown to have decreased blood vasopressin levels. The specification discloses monoclonal antibody #23-57-137-1 that binds specifically to N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 is produced by hybridoma deposited as FERM BP-5631. The deposit has been made under the terms of the Budapest Treaty on August 15, 1996 at the National Institute of Bioscience and Human-technology Agency of Industrial Science and Technology, Japan (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan) under the accession No. FERM BP-5631 as indicated at page 24. A declaration by Masao Haruna filed October 20, 2004, who is associated with the patent owner, stating that the hybridoma FERM BP-5631 secreting the antibody #23-57-137-1 has been deposited under the Budapest Treaty and that said hybridoma FERM BP-5631 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent had satisfied the deposit requirement made herein. The specification further discloses a method of making chimeric or humanized #23-57-137-1 thereof that binds specifically to human PTHrP 1-34 consisting of the amino acid sequence of SEQ ID NO: 75 for inhibits the binding of PTHrP to

its receptor and thereby ameliorates the low blood vasopressin levels associated with cancer such as mice implanted with human large cell lung carcinoma LC-6, which is a human hypercalcemia model (see Figure 1). The specification discloses anti-PTHrP antibody can be conjugated to e.g., polyethylene glycol; PEG), see page 13 at last line. The specification also discloses various humanized light chain versions of the antibody such as the ones disclosed at page 62.

The specification does not teach how to make any humanized antibody or binding fragment thereof having any amino acid substitutions or chemical modification other the conjugating PEG for the claimed method (claim 4).

The specification exemplifies humanized antibody having the specific substitution in the framework regions of the immunoglobulin light chain, see example 5, pages 67-69. With respect to chemical modification, the specification discloses only chemically conjugating antibody to the polyethylene glycol (PEG) to extend the half-life of the antibody or antibody fragment.

Other than humanized antibody having the specific amino acid substitution at the specified positions in the light chain identifiable by SEQ ID NO at pages 50 and 61 and conjugated said antibody or binding fragment thereof to polyethylene glycol (PEG), the specification does not teach how to make any modified antibody having any amino acid substitution or any chemical modification such that the modified antibody still binds specifically to SEQ ID NO: 75 for the claimed methods. There is insufficient guidance as to which amino acids within the full-length sequence of the heavy chain of any humanized monoclonal antibody anti-PTHrP to be substituted and whether such substitution retains binding specificity to SEQ ID NO: 75. Given the numerous amino acid substitutions, there is insufficient *in vivo* working examples showing the modified humanized monoclonal antibody anti-PTHrP still binds specifically to SEQ ID NO: 75, in turn, effective to treat or increase the low blood vasopressin levels as a resulted from cancer.

The state of the prior art as exemplified by Abaza *et al*, of record, is such that even a single amino acid substitution outside the antigenic site can exert drastic effects on the binding specificity of a protein with monoclonal antibody against the site (See abstract, in particular).

Kobrin et al (of record, J Immunology 146: 2017-2020, 1991; PTO 892) teach that a single amino acid substitution from aspartic acid to asparagine at residue 95 of the heavy chain variable region of a phosphocholine binding monoclonal antibody resulted in loss of antigen binding (see entire document, abstract, in particular).

Barrios et al (of record, J Molecular Recognition 17: 332-338, 2004, PTO 892) teach the length of the antibody heavy chain complementarity determining region (CDR3) is critical for antigen specific binding site (see abstract, in particular). Further, the length of the amino acid sequence that linked the CDRs of light and heavy chains (framework sequences) is important in maintaining their required conformation for binding and *in vivo* activity.

Wu et al. (of record, J. Mol. Biol. 294 : 151-162, 1999 ; PTO 892) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

However, the function of an antibody molecule is dependent on its three dimensional structure, which in turn is dependent on its primary amino acid sequence. Changing the amino acid sequence of an antibody in the CDRs may adversely affect its binding activity. Likewise, fragments of the antibody may not retain the appropriate three dimensional structure necessary to foster binding activity. Moreover, a change in the DNA sequence coding for the antibody may affect the ability of the cell containing the DNA sequence to express, secrete or assemble the antibody. There are also critical framework residues which are important in positioning the CDRs for interaction with antigen or which are involved in interactions between the heavy and light chains. Therefore, it is not clear that any amino acid substitutions from either heavy or light chains or any combination thereof will have the asserted utility of binding specifically to human PTHrP (1-34) of SEQ ID NO: 75 without further guidance from the specification. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to antibody or binding fragment thereof having any chemical modification (claims 4 and 19), the specification discloses conjugating antibody to polyethylene glycol or (PEG), see page 13 at last line. The specification does not teach chemically modified antibody fragment. It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody.

The state of the prior art as exemplified by Banerjiee et al (of record, J Immunology 169: 5137-5144, 2002; PTO 892) is such that chemical modification such as reduction and alkylation affect the conformation of the protein-antibody interaction. Banerjiee et al teach disrupting

interchain disulfide bonds between cysteine in close proximity on the protein surface and antigen binding region of antibody such as IgE by reducing agent such as DTT resulted in complete loss of IgE antibody binding to protein (see abstract, page 5141, col. 2, first paragraph, in particular). Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to the phrase "antibody or binding fragment thereof sufficient amount to inhibit a decrease or increase the vasopressin level in blood of the patient" in amended claim 9, inhibiting a decrease or inhibiting an increase vasopressin level in blood of the patient is mutually exclusive.

The specification does not disclose which humanized antibody or binding fragment thereof inhibits a decrease vasopressin level in blood of a patient and which humanized antibody or binding fragment increases vasopressin level in blood of a patient. The declaration by Etsuro Onuma filed August 29, 2008 stated that anti-PTHrP antibody when administered resulted in an increase in blood vasopressin level. Likewise, the problem occurs in claim 26. The specification does not teach administering anti-PTHrP sufficient to decrease the vasopressin level in the blood of the patient.

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed August 29, 2008 and August 5, 2008 have been fully considered but are not found persuasive.

Applicants' position is that Claim 9 defines treating at least one of four specific symptoms-- polyuria, dehydration, mouth dryness and hyperosmolarity, by administering an antibody or binding fragment thereof specifically binding to SEQ ID NO:75. The specification does describe general methods of making antibodies, something which is well-known in the art, and a specific antibody-producing hybridoma (see Claim 6). To treat those symptoms then, all one has to do is administer those antibodies with specifics such as dosages, regimens, etc being determined by the clinician as is customarily the practice based on age, weight, race, gender,

and other physiological factors of the patient. With respect to Claim 26, again the operative step is to administer the antibody that binds to SEQ ID NO: 75, the resulting decrease or increase in vasopressin will follow as is described in the specification.

In response, claim 4 still recites the method according to claim 26, wherein the antibody is any modified antibody and wherein said modification is selected from any amino acid substitution or chemical modification.

The state of the prior art as exemplified by Abaza *et al*, of record, is such that even a single amino acid substitution outside the antigenic site can exert drastic effects on the binding specificity of a protein with monoclonal antibody against the site (See abstract, in particular).

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Kobrin et al. Kobrin et al (J Immunology 146: 2017-2020, 1991; PTO 892) teach that a single amino acid substitution from aspartic acid to asparagine at residue 95 of the heavy chain variable region of a phosphocholine binding monoclonal antibody resulted in loss of antigen binding (see entire document, abstract, in particular).

Barrios et al (J Molecular Recognition 17: 332-338, 2004, PTO 892) teach the length of the antibody heavy chain complementarity determining region (CDR3) is critical for antigen specific binding site (see abstract, in particular). Further, the length of the amino acid sequence that linked the CDRs of light and heavy chains (framework sequences) is important in maintaining their required conformation for binding and *in vivo* activity.

Wu et al. (J. Mol. Biol.294 : 151-162, 1999 ; PTO 892) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Given the innumerous amino acids substitution in the immunoglobulin heavy and/or light chain, it is unpredictable which substitution is associated with maintaining low vasopressin level and which substitution or chemical modification is associated with increasing low vasopressin level in blood or any other tissue such as the hypothalamus of the brain. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to antibody having any chemical modification (claim 4), the specification discloses conjugating antibody to polyethylene glycol or (PEG), see page 13 at last line. The

specification does not teach any chemically modified antibody or any chemically modified antibody fragment. It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody.

The state of the prior art as exemplified by Banerjiee et al (J Immunology 169: 5137-5144, 2002; PTO 892) is such that chemical modification such as reduction and alkylation affect the conformation of the protein-antibody interaction. Banerjiee et al teach disrupting interchain disulfide bonds between cysteine in close proximity on the protein surface and antigen binding region of antibody such as IgE by reducing agent such as DTT resulted in complete loss of IgE antibody binding to protein (see abstract, page 5141, col. 2, first paragraph, in particular).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 4, 7-10 and 26 stand rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,903,194 B1 (of record, filed September 24, 1997; PTO 892).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The '194 patent teaches a method of treating a symptom as a results of cancer such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), anorexia and nausea dehydration due to insufficient uptake of water which are all associated with low blood vasopressin levels (see col. 1, lines 42-61, in particular). The reference method inhibits the binding of PTHrP to its receptor by administering to a patient a monoclonal anti-PTHrP antibody such as a humanized antibody that binds to human PTHrP 1-34, wherein the reference human PTHrP 1-34 is 100% identical to the claimed SEQ ID NO: 75 (see entire document, claim 11 of the '194 patent, col. 7, lines 41-57, reference SEQ ID NO: 75, col. 3, lines 64-65, col. 14, lines 56, claims 1-6 of the '194 patent, col. 10, lines 60-67, col. 30, lines 50, col. 24, lines 10, in particular). The reference monoclonal antibody #23-57-1371 is produced by hybridoma deposited under accession No. FERM BP-5631 (see col. 27, lines 29-36, in particular). The '194 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see col. 46, lines 63 bridging col. 47, lines 1-2, in particular). The '194 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the humanized #23-57-137-1 in the claimed method (see col. 24, line 15, in particular).

Given the reference method administering the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining or increasing the low vasopressin level as claimed (see col. 2, lines 42-52, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed August 29, 2008 and August 5, 2008 and the declaration from Essuro Onuma under 37 C.F.R § 1.132 have been fully considered but are not found persuasive.

Applicants' position is that The fundamental basis for these rejections is that of alleged inherency. Again, the Examiner has noted that art "inherently" achieve the effects on vasopressin levels. However, the Examiner has provided no proof of this. Rather, the Examiner is using Applicants' disclosure against them. As noted by the court in *In re Oelrich,* 666 F.2d 578,581,212 USPQ 323 (CCPA 1981), the mere fact that a certain thing may result from a given set of circumstances is not sufficient to prove inherency. Inherency may not be established by probabilities or possibilities. Something that is inherent must inevitably be the result each and every time.

It is by now well settled that the burden of establishing *a prima facie* case of anticipation resides with the Patent and Trademark Office. *In re Piasecki,* 745 F.2d 1468, 1472, 223 USPQ 785,788 (Fed. Cir. 1984), quoting In *re Warner,* 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967).

As noted by the Board of Patent Appeals and Interferences in *Exparte SMnner, 2* USPQ2d 1788, before an Examiner can switch the burden of proof of showing non-inherency to the applicant, the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the functional limitation is an inherent characteristic of the prior art. In this case, the Examiner has provided no such evidence.

In response, the applied reference has a common assignee but different inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome by an appropriate showing under 37 CFR 1.131.

The '194 patent teaches a method of treating a symptom as a results of cancer such as, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), anorexia and nausea dehydration due to insufficient uptake of water which are all associated with low vasopressin levels (see col. 1, lines 42-61, in particular).

Given the reference method *administering the same antibody to treat the same patient population* via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as increasing the vasopressin blood level as claimed (see col. 2, lines 42-52, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of

malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8).

Although the reference is silent about vasopressin levels in blood, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). {i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable. In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patient is being administered the same active agent, in this case, humanized anti-PTHrP1-34 antibody by the same mode of administration in the same amount in both the instant claims and the cited prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer a monoclonal anti-PTHrP antibody such as a humanized antibody that binds to human PTHrP 1-34, wherein the reference human PTHrP 1-34 is 100% identical to the claimed SEQ ID NO: 75 for treating symptom as a results of cancer such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), anorexia and nausea dehydration due to insufficient uptake of water which are all associated with low blood vasopressin levels as taught by the '194 patent.

8. Claims 4, 7-10 and 26 stand rejected under 35 U.S.C. 102(b) as being anticipated by CA 2,266,332 publication (of record, published April 2, 1998; PTO 892).

The CA 2,266,332 patent teaches a method of treating at least one symptom caused by a decrease in vasopressin levels as a results from cancer such as polyuria and dehydration (see page 2, lines 7-24, page 135, in particular) by administering to patient such as animal or human (see page 49, lines 1-14, in particular) at least one anti-PTHrP such as monoclonal antibody, humanized antibody (see page 14, page 55, page 76, in particular) that binds specifically to human PTHrP1-34 of SEQ ID NO: 75, which is which is 100% identical to the claimed SEQ ID NO: 75 (see paragraph bridging pages 14-15, in particular). The CA 2,266,332 patent teaches monoclonal antibody #23-57-1371 produced by deposited hybridoma FERM BP-5631 (see page 55, line 4, in particular) and humanized antibody #23-57-1371 thereof (see page 49, page 103, and pages 118, 121, in particular). The CA 2,266,332 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the immunoglobulin light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see Table 3 at page 103, paragraph bridging page 97 and 98, in particular). The CA 2,266,332 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the claimed humanized #23-57-137-1.

Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining or increasing the low vasopressin level of patient with cancer (humoral hypercalcemia of malignancy) as claimed in claims 8 and 10 (see page 2 of CA266, page 332, lines 7-24, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments filed August 29, 2008 and August 5, 2008 and the declaration from Mr. Onuma under 37 C.F.R § 1.132 have been fully considered but are not found persuasive.

Applicants' position is that the fundamental basis for these rejections is that of alleged inherency. Again, the Examiner has noted that art "inherently" achieve the effects on vasopressin levels. However, the Examiner has provided no proof of this. Rather, the Examiner is using Applicants' disclosure against them. As noted by the court in *In re Oelrich,* 666 F.2d 578,581,212 USPQ 323 (CCPA 1981), the mere fact that a certain thing may result from a given set of circumstances is not sufficient to prove inherency. Inherency may not be established by probabilities or possibilities. Something that is inherent must inevitably be the result each and every time.

It is by now well settled that the burden of establishing *a prima facie* case of anticipation resides with the Patent and Trademark Office. *In re Piasecki,* 745 F.2d 1468, 1472, 223 USPQ 785,788 (Fed. Cir. 1984), quoting In *re Warner,* 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967).

As noted by the Board of Patent Appeals and Interferences in *Exparte SMnner, 2* USPQ2d 1788, before an Examiner can switch the burden of proof of showing non-inherency to the applicant, the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the functional limitation is an inherent characteristic of the prior art. In this case, the Examiner has provided no such evidence.

It is Applicants' position that the treatment of hypercalcemia bears no immediate relationship to vasopressin levels in blood. That is, the present application is the first to show that PTHrP causes a decrease in vasopressin level in blood, and that administration of anti-PTHrP antibody increase in vasopressin levels in blood. Applicants are to provide experimental results demonstrating that anti-PTHrP antibody when administration resulted in an increase in vasopressin. However, if administered Alendronate (sodium [4-amino-1-hydroxy-1-(hydroxy-oxido-phosphoryl)- butyl]phosphonic acid trihydrate), this did not effect vasopressin levels in the blood. Alendronate is a typical therapeutic agent for treating humoral hypercalcemia of malignancy (HHM) thus indicting that therapeutic effects on HHM bears no immediate relationship to vasopressin in the blood.

Further, the art does not provide any insight into treating patients having at least one symptom selected from the group consisting of polyuria, dehydration, mouth dryness and hyperosmolarity (see Claim 9 and Claim 29).

Contrary to applicant's assertion that the art does not teach treating patients having at least one symptom selected from the group consisting of polyuria, dehydration using humanized anti-PTHrP or binding fragment thereof, the CA 2,266,332 patent teaches a method of treating at least one symptom as a results from cancer such as **polyuria and dehydration** (see page 2, lines 7-24, page 135, in particular) by administering to patient such as animal or human (see page 49, lines 1-14, in particular) at least one anti-PTHrP such as monoclonal antibody, or humanized monoclonal antibody (see page 14, page 55, page 76, in particular) that binds specifically to human PTHrP1-34 of SEQ ID NO: 75, which is which is 100% identical to the claimed SEQ ID NO: 75 (see paragraph bridging pages 14-15, in particular). The hypercalcemia model used in the specification and the declaration from Mr. Onuma (nude mice transplanted with human tumor large cell lung carcinoma LC-6) is the same hypercalcemia model (a human tumor LC-6 transplanted nude mouse) in the '332 patent (see page 114, lines 1-2, page 115, line 1-2, in particular).

The CA 2,266,332 patent teaches the reference monoclonal antibody #23-57-1371 is produced by the deposited hybridoma FERM BP-5631 (see page 55, line 4, in particular) and humanized antibody #23-57-1371 (see page 49, page 103, and pages 118, 121, in particular). Note, the reference humanized antibody #23-57-1371 is the same humanized antibody disclosed in instant application, See pages 5, and 11-12 of instant specification.

The CA 2,266,332 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the immunoglobulin light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see Table 3 at page 103, paragraph bridging page 97 and 98, in particular). The CA 2,266,332 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the claimed humanized #23-57-137-1. Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as increasing low vasopressin level in blood of the patient and symptoms such as polyuria and dehydration as a resulted of decreased blood vasopressin levels in the hypercalcemia animal model as claimed (see page 2 of CA266,332, lines 7-24, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin

level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

Although the reference is silent about vasopressin levels, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). {i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable. In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patient is being administered the same active agent, in this case, humanized anti-PTHrP1-34 antibody by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer a monoclonal anti-PTHrP antibody such as a humanized antibody that binds to human PTHrP 1-34, wherein the reference human PTHrP 1-34 is 100% identical to the claimed SEQ ID NO: 75 for treating symptom as a results of cancer such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), anorexia and nausea dehydration due to insufficient uptake of water which are all associated with low blood vasopressin levels as taught the CA 2,266,332 patent.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 4, 25 and 26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,903,194 B1 (of record, filed September 24, 1997; PTO 892) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of the '194 patent have been discussed supra. The '194 patent teaches the antibody that binds to PTHrP is useful for treating the symptoms associated with humoral hypercalcemia of malignancy with higher therapeutic effects and less side-effects upon consecutive used (see col. 2, lines 42-57, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of increasing blood vasopressin level wherein the humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor to blood ratio (see page 1388, page 1392, in particular). However, $F(ab')_2$ antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody by conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) would extends the *in vivo* half life of the antibody in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to chemically modified the humanized antibody fragment such as $F(ab')_2$ of the '194 patent with the polyethylene glycol as taught by Kitamura et al with the expectation that it will improve the in vivo half-life of the antibody.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment is that PEG conjugation extends the half life of the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The '194 patent teaches humanized antibody and binding fragment thereof that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed August 29, 2008 and August 5, 2008 and the declaration from Mr. Onuma under 37 C.F.R § 1.132 have been fully considered but are not found persuasive.

Applicants' position is that anti-PTHrP antibody when administered resulted in an increase in vasopressin. However, if administered Alendronate, this did not affect vasopressin levels in blood. Alendronate is a typical therapeutic agent for treating humoral hypercalcemia of malignancy (HHM) thus indicating that the therapeutic effects on HHM bears no immediate relationship to vasopressin in the blood.

In response, Alendronate is used for treating osteoporosis or hypercalcemia (high serum calcium levels) as a results of elevated parathyroid hormone in hyperparathyroidism. It is expected that Alendronate has no effect on vasopressin level because parathyroid hormone is not the same protein as parathyroid related protein 1-34 of SEQ ID NO: 74, which affects vasopressin levels in blood.

The rejection of the claimed method of administering the full-length anti-PTHrP1-34 antibody to a hypercalcemia model in the '194 patent have been discussed.

The invention in claim 4 differs from the teachings of the reference only in that the method of increasing blood vasopressin level wherein the humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor to blood ratio (see page 1388, page 1392, in particular). However, $F(ab')_2$ antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody by conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) would extends the *in vivo* half life of the antibody in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to chemically modified the humanized antibody fragment such as $F(ab')_2$ of the '194 patent with the polyethylene glycol as taught by Kitamura et al with the expectation that it will improve the in vivo half-life of the antibody.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment is that PEG conjugation extends the half life of the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The '194 patent teaches humanized antibody and binding fragment thereof that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

12. Claims 25-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,903,194 (of record, filed March 25, 1999: PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of the '194 patent have been discussed supra.

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody fragment is $(Fab')_2$, scFv or Fv instead of whole humanized monoclonal antibody that binds specifically to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using the humanized PTHrP antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The '194 patent teaches the PTHrP antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or dehydration, that caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin levels (see col. 60, line 6-18, in particular).

13. Claims 4, 7-10, 25 and 26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2,266,332 patent (of record, published April 2, 1998; PTO 892) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of CA 2,266,332 patent have been discussed supra. The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP of SEQ ID NO: 75 is less immunogenic and useful in treating the symptoms associated with humoral

hypercalcemia associated with malignancy with higher therapeutic effects and less side-effects upon consecutive used (see page 14, page 133, and page 135, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is $F(ab')_2$ fragment instead whole humanized anti-PTHrP (1-34) antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole humanized anti-PTHrP (1-34) antibody that binds specifically to SEQ ID NO: 75.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, $F(ab')_2$ antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody fragment $F(ab')_2$ by conjugating to polyethylene glycol (PEG) will extend the half-life of the antibody fragment in circulation (see page 1393, first paragraph, paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of $F(ab')_2$ fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to chemically modified antibody fragment such as $F(ab')_2$ that binds to SEQ ID NO: 75 of the CA 2,266,332 patent by conjugating the antibody fragment to polyethylene glycol as taught by Kitamura et al.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified such antibody fragment with PEG is that PEG extends the half-life of the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP

is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Applicants' arguments filed August 29, 2008 and August 5, 2008 and the declaration from Mr. Onuma under 37 C.F.R § 1.132 have been fully considered but are not found persuasive.

Applicants' position is that anti-PTHrP antibody when administered resulted in an increase in vasopressin. However, if administered Alendronate, this did not effect vasopressin levels in blood. Alendronate is a typical therapeutic agent for treating humoral hypercalcemia of malignancy (HHM) thus indicating that the therapeutic effects on HHM bears no immediate relationship to vasopressin in the blood.

In response, Alendronate is used for treating osteoporosis or hypercalcemia (high serum calcium levels) as a results of elevated parathyroid hormone in hyperparathyroidism. It is expected that Alendronate has no effect on vasopressin level because parathyroid hormone is not the same protein as parathyroid related protein 1-34 of SEQ ID NO: 74, which affects vasopressin levels in blood.

The teachings of CA 2,266,332 patent have been discussed supra. The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP of SEQ ID NO: 75 is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side-effects upon consecutive used (see page 14, page 133, and page 135, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the humanized anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is $F(ab')_2$ fragment instead whole humanized anti-PTHrP (1-34) antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole humanized anti-PTHrP (1-34) antibody that binds specifically to SEQ ID NO: 75.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, $F(ab')_2$ antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody fragment $F(ab')_2$ by conjugating to polyethylene glycol (PEG) will extend the half-life of the antibody fragment in circulation (see page 1393, first paragraph, paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of $F(ab')_2$ fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to chemically modified antibody fragment such as $F(ab')_2$ that binds to SEQ ID NO: 75 of the CA 2,266,332 patent by conjugating the antibody fragment to polyethylene glycol as taught by Kitamura et al.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified such antibody fragment with PEG is that PEG extends the half-life of the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

14. Claims 25-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2,266,332 patent (of record, published April 2, 1998; PTO 892) in view of Harlow *et al* (of record, in

Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of CA 2,266,332 patent have been discussed supra. The CA 2,266,332 patent teaches the humanized antibody is less immunogenic and is useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular).

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole humanized antibody that binds to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are that it is small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the humanized antibody that binds to SEQ ID NO: 75 of CA 2,266,332 patent as starting material to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent for use in a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the CA 2,266,332 patent.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced

cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The CA 2,266,332 patent teaches the reference humanized antibody that binds to human PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

16. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

17. Claims 4, 7-10, and 26 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. US Pat No 6,903,194 B1.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the issuance of a patent to instant claims which drawn to a method of inhibiting the binding between PTHrP and its receptor by administering a genus of substance such as monoclonal antibody, humanized antibody, chimeric antibody, human antibody or binding fragment thereof that binds to human PTHrP (1-34) of SEQ ID NO: 75 as well as monoclonal antibody produced by the hybridoma deposited as FERM BP-5631, wherein the low vasopressin levels as resulted from malignant cancer would include the method of inhibiting the binding between PTHrP and a receptor thereof in claim 11 of the '194 patent comprising administering the humanized antibody that binds specifically to human PTHrP1-34 of the issued patent (species) wherein the humanized antibody is an agent for suppressing hypercalcemia or hypophosphatema associated with malignant tumor.

Further, given the method of the '194 patent teaches the same antibody to treat the same patient population, the method of the '194 patent inherently has the same effects such as maintaining or increasing low vasopressin level wherein the low levels of vasopressin is associated with cancer. As defined in instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Claim 4 is included in this rejection because the '194 patent also teaches modified antibody by amino acid substitution such as version b of the humanized antibody (see col. 46, lines 63 bridging col. 47, lines 1-2, in particular). Claim 6 is included in this rejection because the '194 patent also teaches antibody produced by the same deposited hybridoma FERM BP-5631 (see col. 27, lines 29-36, in particular).

The Examiner acknowledged that Applicants will consider filing a terminal disclaimer once patentable subject has been indicated in this case.

18. Claims 4, 7-10, 25 and 26 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,903,194 B1 (of record) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of the '194 patent have been discussed supra. The '194 patent teaches the antibody that binds to PTHrP is useful for treating the symptoms associated with humoral hypercalcemia of malignancy with higher therapeutic effects and less side-effects upon consecutive used (see col. 2, lines 42-57, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 9 differs from the teachings of the reference only in that the method of treating at least one symptom caused by a decrease in vasopressin level comprising administering to the patient a binding fragment of an anti-PTHrP antibody instead of a whole antibody.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, F(ab')2 antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody such as conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) or whole antibody (see page 1393, first paragraph, in particular). The advantages of PEG conjugated antibody or antibody binding fragment thereof are that PEG reduces the immunogenicity of any monoclonal antibody as well as extending the half life of the antibody, especially the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as $F(ab')_2$ and then chemically modify the

antibody F(ab')$_2$ fragment or any antibody by conjugating the antibody fragment or antibody to polyethylene glycol as taught by Kitamura et al using the whole monoclonal antibody, humanized antibody, chimeric antibody or human antibody that bind specifically to PTHrP of SEQ ID NO: 75 for a method of maintaining or increasing low vasopressin level by inhibiting the binding of PTHrP to its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as F(ab')$_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The '194 patent teaches antibody such as monoclonal, humanized, chimeric or human antibody that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules leas to hyperuresis (polyuria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular).

The Examiner acknowledged that Applicants will consider filing a terminal disclaimer once patentable subject has been indicated in this case.

19. Claims 25-26 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,903,194 B1 in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of the '194 patent have been discussed supra.

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole antibody that binds specifically to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using the monoclonal, human antibody, chimeric or humanized PTHrP antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The '194 patent teaches the PTHrP antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or

dehydration, that caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin levels (see col. 60, line 6-18, in particular).

The Examiner acknowledged that Applicants will consider filing a terminal disclaimer once patentable subject has been indicated in this case.

20. The following new ground of rejection is necessitated by the amendment filed August 29, 2008.

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

22. Claims 4, 8-10, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 9 and 26 fail to correspond in scope with that which applicant(s) regard as the invention can be found in the reply filed August 29, 2008. In that paper, applicant has stated the present application is the first to show that PTHrP causes a decrease in vasopressin level in blood, and that administration of *anti-PTHrP antibody increases in vasopressin levels in blood*, and this statement indicates that the invention is different from what is defined in the claim(s) because amended claim 9 recite administering humanized anti-parathyroid hormone related protein 1-34 or binding fragment thereof in an amount sufficient to *inhibit a decrease the vasopressin level* in the blood of a patient. Amended claim 26 recites a method of inhibit a decrease vasopressin level in blood ... in an amount sufficient to *decrease the vasopressin level* in the blood of the patient. Finally, the declaration by Onuma under 37 C.F.R § 1.132 states that "the concentration of vasopressin in blood increase to 711.1 ± 141.3 (pg/ml) with administration of anti-PTHrP antibody in the hypercalcemia model animals.

23. No claim is allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

26. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
December 19, 2008